REMARKS

Claims 27-43 were pending in the present application. By virtue of this response, claim 44 has been added. Support for added claim 44 is found in the specification, *inter alia*, in Example 4 on page 29, line 4 to page 30, line 6; and in Example 5 on page 31, line 6 to page 32, line 12. Accordingly, claims 27-44 are currently under consideration. No new matter has been added.

The specification is amended to correctly specify the priority data of the instant application under the section "Cross-Reference to Related Applications." No new matter is added and entry of the amendments to the specification and claims is respectfully requested.

Reconsideration of the application is respectfully requested in view of the above amendments and the following remarks. For the Examiner's convenience, the various bases for rejection are presented in the order in which they were raised in the Office Action.

A. Rejections under 35 USC § 101

Claims 27-31 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter. Specifically, the Examiner is of the view that these claims are unpatentable because they "claim a product of Nature, rather than a composition made by a person, because a composition cannot properly comprise an "isolated" polynucleotide." Office Action, page 3. Applicants respectfully traverse.

Independent claims 27 specifies a "composition comprising an isolated polynucleotide which encodes an hepatitis C virus (HCV) proteolytic polypeptide" (emphasis added). The Utility Examination Guidelines of the United States Patent and Trademark Office state that "DNA molecules are eligible for patents when *isolated from their natural state*," at least when the isolation process involves purifying steps that "separate the gene from other molecules naturally associated with it." 66(4) Fed. Reg. 1092, 1093 (emphasis added), effective January 5, 2001.[1] Thus, an

[1] Relevant pages of the Guidelines are attached as Exhibit E1.

The ordinary meaning of "purify" is to "free from undesirable elements." (Merriam-Webster's Collegiate Dictionary, 10th ed. 2002. Merriam-Webster, Inc. Springfield, MA) Therefore, a "purified" substance can exist in a composition so long as it is free from undesirable elements. The verb "to isolate" is defined as "to separate from another

isolated or purified polynucleotide "that has the same sequence as a naturally occurring gene" is patentable because that polynucleotide "does not occur in that isolated form in nature." *Id. See Diamond v. Chakrabarty* 447 US 303, 309; 206 USPQ 193, 197 (1980). The words "isolated" or "purified" distinguish the claimed polynucleotide from the polynucleotide as it exists in nature, i.e., unisolated or unpurified.

Further, the Manual for Patent Examining Procedure states that "when claims are directed to any purified and isolated DNA sequence encoding a specifically named protein where the protein has a specifically identified sequence, a rejection of the claims as broader than the enabling disclosure is generally not appropriate because one skilled in the art could readily determine any one of the claimed embodiments." MPEP 2164.08.

Since claim 27 specifies an "isolated polynucleotide" it cannot be construed by the Examiner to comprise the hepatitis C virus in its natural state. Accordingly, the "isolated" polynucleotide of claim 27 is a non-naturally occurring form and can exist as a component of a composition. Claims 28-31 depend from independent claim 27. Therefore, applicants respectfully request that the rejection against claims 27-31 under 35 U.S.C. § 101 for being non-statutory subject matter, be withdrawn.

B. Non-statutory Double Patenting Rejection

(a) Claims 27-43 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,371,017.

Applicants submit that they will file a terminal disclaimer in the present application to disclaim any term beyond the term of the earlier expiring patent in order to overcome this ground for rejection, after the conflicting claims are found to be allowable.

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substance so as to obtain pure or in a free state." (Merriam-Webster's Collegiate Dictionary, 10th ed. 2002. Merriam-Webster, Inc. Springfield, MA; Exhibit E2)

(b) Claim 36 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 10/438,313, which is an application for reissue of U.S. Patent No. 5,371,017.

Applicants submit that they will file a terminal disclaimer in the appropriate case—the present application or copending Application No. 10/438,313 – to disclaim any term beyond the term of the earlier expiring patent in order to overcome this ground for rejection, after the conflicting claims are found allowable.

C. Rejections under 35 USC § 112

a. Rejections under 35 U.S.C. §112, first paragraph – written description

Claims 27, 32, 33, 37, 42, and 43 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically the Examiner contends that the specification fails to exemplify or describe the preparation of the polynucleotides of claim 27, or recite any structural features of, a generic "proteolytic hepatitis C virus polypeptides" recited by the claims. Office Action, page 5. This conclusion is based on the grounds that the specification fails to identify a polynucleotide encoding an amino acid sequence that constitutes a proteolytic HCV polypeptide with an NS3 domain. *Id.* The Examiner also contends the following: the application fails to disclose a polynucleotide encoding any HCV polypeptide or corresponding fusion protein (either comprising the sequence of page 21, lines 13-15 or some other); example 5 suggests that proteolytic products detected by ELISA could only be produced by endogenous proteases; examples 6 and 8-10 are hypothetical; and, no "relevant identifying characteristics" of a proteolytic HCV protease is shown. *Id.* at 5.

Applicants respectfully traverse for the following reasons:

(i) (i) A Written Description of an "isolated polynucleotide" encoding an HCV proteolytic polypeptide comprising an HCV NS3 domain protease or an active truncation analog is provided.

"[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

(a) An NS3 domain is described in the specification

The specification states that: "[t]he term 'HCV protease' refers to an enzyme derived from HCV which exhibits proteolytic activity, specifically the polypeptide *encoded* in the [polynucleotide sequence of the] NS3 domain of the HCV genome." (Specification, page 6, lines 22-25) (emphasis added). The polynucleotide sequence encoding an HCV NS3 domain protease sequence is provided in Figure 1. (Specification, page 3, line 7). The specification points to a specific section in the NS3 domain as the key to proteolytic activity and notes that the termini of the relevant section are putative. (Specification, page 6, line 24 through page 7, line 21). The specification describes a polynucleotide encoding an NS3 domain of HCV. Page 8, lines 7-25 refer to NS3 domain within the sequence of HCV by analogy with the Yellow Fever Virus (a flavivirus) polyprotein. An HCV protease encoded by the NS3 domain in at least one strain of HCV is further described with reference to a 202 amino acid protease sequence from SEQ ID NO: 1 in page 6, line 22 to page 7, line 18 (*see* SEQ ID NO: 65); the corresponding polynucleotide sequence is disclosed in Figure 1.

An "active" truncation analog is one that exhibits proteolytic activity, a property that one can ascertain by running a limited number of standard experiments. The specification describes how one would determine the structure of the shortest active HCV NS3 protease by truncation analysis involving routine methods. (Specification, page 7, line 27 – page 8, line 6).

In a European patent application EP 318,216A1 (published May 31, 1989), the inventors of the present application had previously reported[2] the nucleotide sequence of the HCV genome and identified a similarity between a 530 amino acid domain of the HCV polyprotein sequence and the NS3 protein sequence of dengue virus, a flavivirus. (p. 52, sec. IV.H.3 and Figs. 41-1 and 41-2). Likewise, in PCT application WO 89/04669 a correlation between HCV polyprotein and a nonstructural protein of the flavivirus was noted. (p. 128, sec. IV.H.3). The disclosures of both WO 89/04669 and EP 318,216 (Houghton et al.) are incorporated by reference in the instant specification at page 4, lines 4-8.

Polynucleotides encoding NS3 domains in flaviviruses such as yellow fever virus were known in the art. (*see* Fig. 1 and page 731 in Rice CM *et al.*, Science, 229(4715):726-733 (1985)). EP 388,232 by the same inventive entity as the current application and published September 19, 1990, identified the NS3 domain in comparison with flaviviruses. (pages 33-34 of EP 388,232). Other publications identifying the nucleotide sequence corresponding to an NS3 domain protease of HCV were available prior to the filing of the priority application of the current application. Computer aided comparative analysis of the polyproteins of several flaviviruses was known to have sequence similarity with HCV in the NS3 region. (Miller *at al.* Proc. Natl. Acad. Sci. 87:2057-2061, at 2060 and Fig. 3 (March 1990)). Yoneyama *et al.* disclose the use of PCR primer from the NS3 region of HCV for detection of viral sequences. (Jpn. J. Med. Sci. Biol. 43:89-94 (1990)).[3]

(b) An NS3 domain protease is disclosed in the specification.

Independent claim 27 specifies a composition comprising an isolated polynucleotide encoding a hepatitis C virus polypeptide which itself comprises "an HCV NS3 domain protease or an active HCV NS3 domain protease truncation analog." Independent claim 32 specifies a composition comprising a corresponding fusion protein. Independent claim 37 specifies an expression vector for producing an HCV proteolytic polypeptide in a host cell, comprising a similar polynucleotide as in claim 27. The remaining dependent claims are generally limited to truncation

[2] EP 318,216A1 was filed on Nov. 11, 1988 and published May 31, 1989, prior to the earliest priority date of this application.

analogs containing the sequence of SEQ ID NOS: 63-65. The claims are not directed to a specific kind of protease activity, they are directed to *any* protease activity encoded by the NS3 region.

Various polynucleotides encoding a fusion protein containing hSOD fused to an NS3 domain or truncation analog are disclosed in Example 4. (Specification, page 29, line 7 through page 30, line 6). Most of these polynucleotides are shown to encode a polypeptide with proteolytic activity, as determined by self cleavage of SOD - HCV protease fusion proteins expressed in *E. coli*.[4]

- The P190 polynucleotide encoding amino acids 1-199 of the HCV protease (page 29, lines 19-20) showed no protease cleavage activity (Specification, page 32, lines 8-12).
- P300 which encodes amino acids 1-299 of HCV protease (page 29, lines 25-26) indicated occurrence of cleavage (Specification, page 32, lines 1-7).
- P500 encoding amino acids 1-513 of Fig. 1 (page 30, lines 4-6) indicated occurrence of cleavage (Specification, page 31, lines 22-25).
- The fusion protein ("P600") encoded by the vector cf1SODp600 which includes amino acids 1-686 of Fig. 1 also showed proteolytic activity. (Specification, page 31, lines 12-17).
- The specification concludes that "the minimum essential sequence for HCV protease extends to the region between amino acids 199 and 299." (Specification, page 32, lines 10-12).

The Examiner incorrectly assumes that the proteolytic cleavage described in Example 5 is attributable *solely* to the host cells' endogenous proteases. Only in subsection A of Example 5 which describes the protease activity of the P600 fusion protein resulting in "34, 53 and 66 kDa"

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[3] Courtesy copies of the references mentioned in the response are attached as Exhibit H for the Examiner's convenience. Only the relevant pages of EP 388,232, WO 89/04669 and EP 318,216 are enclosed.

[4] "The results indicated the occurrence of cleavage, as no full length product (theoretical M_r = 93 kDa) was evident on the gel." (Specification, page 31, lines 12-13).

bands, the 53 and 66 kDa bands are surmised to have undergone "varying degrees of (possibly bacterial) processing" as the predicted product of theoretical M_r = 93 kDa was not observed. (Specification, page 31, lines 13-17).

Protease activity attributable to the NS3 region was evident in the P300 and P500 fusion proteins and no "possibly bacterial" processing is suggested in Examples 5 (B) and (C) as the predicted proteolysis products of theoretical M_r = 51 and 73 kDa respectively were observed. (Specification, page 31, lines 22-25, and page 32, lines 1-2). That the protease activity resides in the HCV NS3 region is confirmed by the observation in Example 5(C), where the P190 fusion product encoding amino acids 1-199 of the HCV protease did not show any protease cleavage activity. (Specification, page 32, lines 8-12).

(c) A peptide substrate for the NS3 domain protease is provided in the specification

The Examiner further contends that the application fails to disclose a polynucleotide that is capable of encoding a proteolytic HCV peptide that could cleave any peptide substrate. Applicants respectfully traverse and submit that a peptide substrate for a HCV NS3 associated protease is disclosed in the specification. The protease activity described in Examples 5 (A), (B), and (C) was observed through self-cleavage of an hSOD-HCV fusion protein wherein the HCV peptide portion corresponded to amino acids 1-686 of Fig. 1 and various truncations thereof. Observance of specific cleavage within the NS3 region is described in every instance where protease activity was observed. For example, "34 kDa band correspond[ing] to the hSOD partner (about 20 kDa) with a portion of the NS3 domain" was observed in each case with the P600, P300 and P500 fusion proteins of NS3 fused to a hSOD leader. (Specification, page 31, lines 15-16).

Applicants submit that the specification describes polynucleotides encoding a protease activity specifically associated with the NS3 region and provides disclosure of a substrate for such protease activity. Thus one of skill in the art would have identified polynucleotides encoding an NS3 domain described in the specification and understood that at the time of filing of the application, the inventors had possession of the claimed invention. Therefore, applicants

respectfully request withdrawal of this ground for rejection for lack of written description under 35 U.S.C. § 112, first paragraph.

(d) NS4A is not essential for the activity of an NS3 domain hepatitis C virus protease or truncation analog

The Examiner refers to several references submitted in an IDS by the Applicants to contend that NS3 domain hepatitis C virus protease requires another region termed NS4A. Applicants respectfully traverse.

The claims of the current application generally specify a composition comprising a polynucleotide encoding a hepatitis C virus polypeptide which itself comprises "an HCV NS3 domain protease or an active HCV NS3 domain protease truncation analog." The claims are not directed to a specific kind of protease activity but any protease activity encoded by the NS3 region. The claims do not specify a particular kind of protease. The NS4A cofactor referred by the Examiner relates to the activity of a "serine protease activity" encoded by the NS3 region. The specification clearly demonstrates a protease activity associated with a protein comprising amino acids 1-299 of HCV protease (*see* Example 5(C)). While a serine protease activity also encoded within this region may require a NS4A cofactor, applicants' claims are directed to any protease activity within the NS3 region. Further, applicants note that "while NS4A appears to be absolutely required for *trans*-cleavage at the 4B/5A site, it is not an essential cofactor for serine protease activity." (*see* Lin *et al.*, J. Virol. 68(12): 8147-8157 (1994), Abstract, lines 10-11, and page 8151, right col. (first full paragraph)). Further *cis*-cleavage by NS3 domain proteases do not require NS4A. (Lin *et al.* p. 8149, right col.; p. 8152, right col.; Fig. 7A; p. 8155, left col.).

Applicants submit that the specification describes a protease activity specifically associated with the NS3 region and provides disclosure of a substrate for such protease activity. Thus one of skill in the art would have identified the NS3 domain described in the specification and understood that at the time of filing of the application, the inventors had possession of the claimed invention. Therefore, applicants respectfully request withdrawal of this ground for rejection for lack of written description under 35 U.S.C. § 112, first paragraph.

D. Rejections under 35 U.S.C. §112, first paragraph – enablement

Claims 27-43 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the Examiner contends that while appropriate analogies are made in the specification between SEQ ID NO: 66, serine protease characteristics, and analogous regions in other flaviviruses, no guidance is provided for making polynucleotides that encode such a protease. The Examiner states that the specification "does not describe, thus cannot enable, an integral hepatitis C virus protease capable of cleaving a defined substrate." (Office Action, page 7). The Examiner also states that the small peptides specified in claims 29, 30, 34, 35, 39 and 40 (*i.e.*, of SEQ ID NOS: 63 and 64) "are insufficient to support proteolysis even if Applicants' disclosure had provided guidance for finding regions of" the HCV genome that could provide such activity. *Id.*

Applicants respectfully traverse these grounds for rejection. To be enabling, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. (*Genentech Inc. v. NovoNordisk A/S*, 108 F.3d 1361, 42 USPQ2d 1001 (Fed. Cir. 1997)).

(a) Applicants submit that the Wands factor cited by the Examiner, *i.e.*, specific guidance about the portion of the HCV polyprotein responsible for recognition of native cleavage sites in the polyprotein, is satisfied in the specification. Specifically, a truncation analysis is described in Example 5, wherein a minimal region between 199-299 amino acids of Fig. 1 is shown to have protease activity, with specific cleavage occurring within the HCV NS3 portion of the hSOD-HCV fusion protein. (Specification, page 32, lines 1-12 and page 29, lines 15-26).

As submitted above, the specification identifies a HCV NS3 region. As described in Example 5, a protease activity is shown to be associated with amino acids 1-299 of Fig. 1 (P300 fusion protein; specification, page 29, lines 15-26 and SEQ ID NO: 66). Example 5 also shows that no protease activity is observed within amino acids 1-199 of Fig. 1 (P190 fusion protein; page 29, lines 15-26, and SEQ ID NO:67). SEQ ID NO: 65 extends between amino acids 60 and 262 of Fig. 1. Thus the amino acid sequence essential for the protease activity is located within amino acids 200 through 262 of the given sequence. One of skill in the art has only a definite and specific region of

the amino acid sequence to identify the protease activity and is able to do so without undue experimentation.

The Examiner also states that the small peptides specified in claims 29, 30, 34, 35, 39 and 40 (*i.e.*, of SEQ ID NOS: 63 and 64) "are insufficient to support proteolysis even if Applicants' disclosure had provided guidance for finding regions of" the HCV genome that could provide such activity. SEQ ID NOS: 63 and 64 specify 11 and 9 amino acid sequences within SEQ ID NO: 65. They are specified in dependent claims 29 and 30 which depend from independent claim 27; in dependent claims 34 and 35 which depend from independent claim 32; and in dependent claims 39 and 40 which depend from independent claim 37. Independent claim 27 specifies a composition comprising an isolated polynucleotide which encodes a hepatitis C virus (HCV) proteolytic polypeptide, "wherein said polypeptide comprises .... [a] NS3 domain protease or . . . active truncation analog." (emphasis added). Independent claim 32 specifies a composition comprising a polynucleotide encoding a fusion protein which similarly "comprises" an NS3 domain protease or active truncation analog. Independent claim 37 specifies an expression vector that "comprises" a polynucleotide encoding an HCV polypeptide which "comprises" an NS3 domain protease or active truncation analog. Thus, the polynucleotides of claims 29, 30, 34, 35, 39 and 40 can contain HCV-derived sequence not limited to SEQ ID NOS: 63 and 64.

SEQ ID NOS: 63 and 64 span 11 and 9 amino acid sequences within SEQ ID NO:65 and are within the protease domain of amino acids 200 and 262 of the given sequence of Fig. 1. Further, SEQ ID NOS: 63 and 64 span a histidine and a serine containing region respectively of sequences homologous to regions responsible for serine protease catalytic activity in Yellow Fever Virus, West Nile Fever virus, Murray Valley Fever virus, and Kunjin virus (Table 1) and in the well-characterized serine proteases: protease A from *Streptomyces griseus*, α-lytic protease, bovine trypsin, chymotrypsin, and elastase (Table 2). (*see* specification, page 8, line 7 – page 9, line 17). Thus, by structural homology and alignment, SEQ ID NOS: 63 and 64 are disclosed in the specification to be associated with protease activity.

While the specification notes characteristic similarities with a serine protease the claims are directed more broadly to a "protease" activity within the NS3 domain. Applicants are not required to correctly set forth, or even know, how and why the claimed NS3 region demonstrates protease activity. *see Enzo Biochem v. Calgene, Inc.*, 188 F.3d 1362, 1375 (Fed. Cir. 1999) ("it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works").

Applicants respectfully request that in view of the description of an NS3 domain, of polynucleotides encoding a protease activity associated with the NS3 domain, and the disclosure of specific examples of such polynucleotides, the rejection for lack of enablement under 35 U.S.C. § 112, first paragraph be withdrawn.

E. Rejections under 35 U.S.C. §112, first paragraph – indefiniteness

a. Indefiniteness of the terms "domain protease" and "truncation analog"

Claims 27-36 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner concludes that independent claims 27 and 31 are indefinite in reciting, "proteolytic hepatits C virus polypeptide . . . compris[ing] an HCV NS3 domain protease or an active . . . truncation analog," because the Specification does not provide a specific, limiting, structural description of a generic NS3 domain protease, and thus one could not determine what is more than the protease and what is a truncation analog.

Applicants respectfully traverse. The application, at page 5, line 20 through page 6, line 4, refers to NS3 domain by analogy with the Yellow Fever Virus polyprotein. An HCV protease encoded by or within the NS3 domain is further described with reference to a 202 amino acid protease within SEQ ID NO: 1 in at least one strain of HCV in page 6, line 26 though page 7, line 18. SEQ ID NO: 65 consists of the corresponding 202 amino acid sequence from Figure 1 (amino acids 60-262).

The protease activity associated with HCV NS3 domain is further characterized in Example 5 (Specification, pages 31-32) as discussed in detail above. The Specification identifies by truncation analysis described in Example 5 a "minimum essential sequence for HCV protease [that] extends to the region between amino acids 199 and 299." (Specification, page 32, lines 10-12).

Further, Examples 4 and 5, as discussed above, disclose active truncation analogs of the HCV NS3 domain protease. The Specification on pages 29-32 disclose a fusion protein P600 including amino acids 1-686 of Fig. 1 which demonstrates protease activity. Active truncation analogs P500 comprising amino acids 1-513 of Fig. 1, and P300 comprising amino acids 1-299 also demonstrate protease activity associated with the NS3 domain. (Specification, page 31, line 5 – page 32, line 7).[5]

Applicants submit that the terms "HCV NS3 domain protease" and "active ... truncation analog" are clearly defined in the Specification and request withdrawal of this ground for rejection.

b. Indefiniteness of the term "isolated"

Claims 27-36 stand rejected as indefinite, since they claim an "isolated" polynucleotide, where no polynucleotide, according to the Examiner, can remain isolated if present in a composition. Applicants respectfully traverse.

Independent claims 27 specifies a "composition comprising an isolated polynucleotide which encodes an hepatitis C virus (HCV) proteolytic polypeptide." (emphasis added). As discussed above in detail under Section A, the term "isolated" polynucleotide is interpreted as a polynucleotide removed from its natural state. The words "isolated" or "purified" distinguish the claimed polynucleotide from the polynucleotide as it exists in nature, i.e., unisolated or unpurified.

Further, throughout the Specification the term "isolated" is used consistent with this meaning of the term. For example, DNA sequences isolated from cDNA libraries (page 18, lines 10-11); isolation of DNA from plasmids in *E. coli* (page 19, lines 18-19; Example 2, page 24:16-18);

[5] Truncation analog P190 comprising amino acids 1-199 does not demonstrate proteolytic activity, and is thus an "inactive" truncation analog. (Specification, page 32, lines 8-10).

isolated restriction fragments (Example 7, page 35, lines 20-21; Example 2, page 25) and elsewhere in the Specification. Example 1 (page 24) discloses the preparation of a HCV cDNA library -- cDNA is by its very nature distinguished from the corresponding DNA found in nature. Several examples of "an isolated polynucleotide which encodes an hepatitis C virus (HCV) proteolytic polypeptide, wherein said polypeptide comprises an HCV NS3 domain protease or an HCV NS3 domain protease active truncation analog," as specified in claim 27 are disclosed in Example 2 (pages 24-26) as a series of DNA expression vectors encoding fusion polypeptides with HCV NS3 domain protease. Compositions such as bacterial or yeast hosts harboring these expression vectors and comprising the claimed polynucleotides are also described in the Specification. (Examples 2 and 7).

Therefore, Applicants submit that an "isolated" polynucleotide is clearly defined in the specification and respectfully request withdrawal of this ground for rejection.

F. Rejections under 35 USC § 102 (b)

a. The reference by Choo et al.

Claims 27-31 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Choo et al., EP 318,216. Applicants respectfully traverse this rejection. This application claims a priority date of April 4, 1990. Choo et al. was published on May 31, 1989. In order to form prior art under 102(b), however, a printed publication must describe the claimed invention "more than one year prior to" the priority date of this application. 35 U.S.C. § 102(b). Because Choo et al. was published less than a year before the priority date of this application, it cannot form prior art under 35 U.S.C. § 102(b).[6] Accordingly, applicants respectfully request that this rejection be withdrawn.

[6] Moreover, it has long been established that, absent a Section 102(b) statutory bar, an inventor's own work cannot be held against him as prior art under 35 U.S.C. § 102(e). Thus, for a reference patent to qualify as prior art under Section 102(e), (1) the application for the reference patent must have been by one who is legally "another" and (2) the filing date of the reference patent must be "before the invention thereof by the applicant ... ." 35 U.S.C. § 102(e). Choo et al. has the same inventorship as this application, and is assigned to the same entity. Since Choo et al. has the same inventorship as this application and does not form prior art against it under Section 102(b), it thus cannot form prior art against this application under Section 102(e).

b. The reference by Reyes et al.

Claims 27-31 also stand rejected under 35 U.S.C. § 102(b) as being anticipated by Reyes et al., WO 90/00597. However, Reyes et al. was published on January 25, 1990, which is not one year prior to this application's claimed priority date of April 4, 1990, as is required in order to form prior art under Section 102(b).

In addition, a prior art reference must disclose each and every limitation of claims 27-31 in order to anticipate them under Section 102. Claims 27-31 cover compositions comprising an isolated polynucleotide containing sequence derived from the NS3 domain protease of HCV. Although Reyes et al. discloses various HCV-derived sequences, none of these appear to encode *any* portion of the NS3 domain protease. Because Reyes et al. fails to disclose each and every limitation of claims 27-31, it cannot anticipate these claims under Section 102.

Since Reyes et al. does not form prior art against this application under Section 102(b) for the above reasons, applicants respectfully request withdrawal of this rejection.

G. Rejections under 35 USC § 103(a)

Claims 27-43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Miyamura et al., U.S. 5,372,928, in view of Miller et al., 1990, Proceedings of the National Academy of Sciences, U.S.A., Vol. 87, pages 2057-2061, Bazan et al., 1989, Virology, Vol. 171, pages 637-639, and Gorbalenya et al., 1989, Nucleic Acids Research, Vol.17, pages 3889-3897, all made of record herewith.

Applicants respectfully traverse this rejection because it does not establish *prima facie* obviousness of the claimed inventions. In particular, the key teachings in the Miyamura patent relied upon in the rejection are not available as prior art against the claimed inventions as a matter of law. Since the Miyamura patent is the primary reference, the rejection should be withdrawn.

The Office Action characterizes the Miyamura patent as follows:

(1) Miyamura et al., see Figures 12A-C, teach a polynucleotide encoding the HCV1 strain polyprotein and the relative positions of both the structural and the non-structural domains within the polyprotein encoded by the nucleic acid sequence of the HCV1 strain, see Miyamura patent, columns 6-7 and Figure 11. Office Action, page 10.

(2) Miyamura et al. teach, at lines 8-10 of col. 7, that the "putative NS3 [domain extends] from about amino acid 1007 to about amino acid 1650'." *Id.* (text within brackets in original).

(3) Miyamura et al. teach, at col. 17, lines 5-21, that functions of domains within the HCV polyprotein may be predicted on the basis of similarities shared by the HCV polyprotein amino acid sequence and flavivirus polyprotein amino acid sequences and that flavivirus NS3 domains have an amino acid sequence region that provides a protease function. Office Action, page 11. According to the Examiner, these teaching have priority to September 15, 1989, when they appeared in the parent application serial No. 07/408,045.

(4) At Examples I-IV at cols. 28-39, Miyamura et al. "teach preparation of cloning vectors, and transformed host cells comprising the vectors, comprising inserts of specific, defined, regions found anywhere in a nucleic acid sequence encoding all or part of an hepatitis C virus polyprotein." *Id.* Miyamura et al. "explicitly teach, at cols. 8-10, that expression vectors comprising transcriptional and translational regulatory elements operably linked to a polynucleotide encoding a desired regions [sic] of the HCV polyprotein should be used to produce desired portions of the hepatitis C virus polyprotein in host cells." *Id.* Miyamura et al. "further suggest preparation of expression constructs providing fusions of hepatitis C virus amino acid sequence regions with proteins commonly used in the art as fusion partners such as β-galactosidase and superoxide dismutase [SOD]" at cols. 14-15. *Id.* (bracketed text in original).

a. The Instant Application Claims Priority to U.S. Patent No. 5,371,017

The instant application has priority of Application No. 07/680,296, filed on April 4, 1991, (now U.S. Patent No. 5,371,017) and its specification is identical to that of the '017 patent.[7] The inventors of the instant application and the '017 patent are identical.

As discussed below, Miyamura et al. is not available as § 102(e) prior art against the '017 patent. Since the instant application claims priority (and contains identical disclosure) to the application from which the '017 patent issued, Miyamura is not available as prior art against the instant application.

b. The Miyamura Patent Cannot be Relied Upon as § 102(e) Prior Art With Respect to the HCV-1 ORF Sequence Information Shown in Figure 12, the Putative Genomic Organization Shown in Figure 11, and the Subject Matter of Column 7, Lines 8-9 and Column 17, Lines 17-21 of the Miyamura Patent

Subject matter disclosed in the Miyamura patent qualifies as prior art under 35 U.S.C. § 103 only if it meets the requirements of 35 U.S.C. § 102(e). The Office Action relies in part on Figure 12, Figure 11 and "cols. 6-7" of the Miyamura patent, stating that the patent teaches a polynucleotide encoding the HCV1 strain's polyprotein and "the relative positions of the structural and the non-structural domains within the polyprotein." Office Action, page 10. The Office Action also relies in part on the Miyamura patent at column 7, lines 8-10, asserting that it teaches there that the "putative NS3 [domain extends] from about amino acid 1007 to about amino acid 1650" (bracketed text in original). *Id.* The Office Action also relies in part on the Miyamura patent at column 17, lines 5-21, stating that the patent there teaches "that functions of domains within the hepatitis C virus polyprotein may be predicted on the basis of similarities shared by amino acid sequence of flaviviruses and the hepatitis C virus amino acid sequence and that a protease function resides in the amino acid sequences of flavivirus NS3 domains." *Id.* at 11.

[7] The instant application, 09/884,455, is a continuation of Application No. 09/253,675, which is a continuation of Application No. 08/709,177 (now U.S. Patent No. 5,885,799), which is a continuation of Application No. 08/440,548 (now U.S. Patent No. 5,597,691), which is a divisional of Application No. 08/350,884 (now U.S. Patent No. 5,585,258), which is divisional of Application No. 07/680,296, filed on April 4, 1991, (now U.S. Patent No. 5,371,017).

(i) Miyamura's Derivation of HCV-1 Subject Matter From The Inventive Entity Of The Instant Application

Applicants note that the Office Action points out that the teachings of the Miyamura patent have priority to September 15, 1989, when they appeared in the parent application 07/408,045. Office Action, page 11. As noted by the Examiner, the Miyamura patent makes clear that the Figure 12 sequence, as well as the genomic organization information set out in Figure 11 and at column 7, lines 8-9, concerns HCV-1. *See* Miyamura patent, column 4, lines 33-36; column 6, line 65 to column 7, line 16. Similarly, the context surrounding the cited material at column 17, lines 16-21 of the Miyamura patent makes clear that this prediction is premised on HCV-1 sequence data. As shown below, this HCV-1 subject matter was derived by the Miyamura inventive entity from the inventive entity of the '017 patent, which is the same inventive entity as the instant application.

Applicants note that the Miyamura patent does not claim any HCV-1 sequences or methods, but rather specifically *disclaims* HCV-1. *See* Miyamura patent, column 40, line 47 to column 42, line 30, claims 1-6 (all of which contain the limitation "wherein said sequence is not homologous to the nucleotide sequence of HCV isolate HCV1"). Similarly, the Miyamura specification makes clear that Miyamura's invention relates to the J1 and J7 HCV isolates, and not to HCV-1. *See, e.g.,* Miyamura patent, column 1, lines 18-19, and column 2, line 34 to column 3, line 65.

As a further evidentiary submission, Applicants provide the Declaration of Tatsuo Miyamura Under 37 C.F.R. § 1.132 ("Miyamura Decl.", Exhibit A hereto, originally submitted during the Reexamination of the '017 patent), who is the first-named inventor on the Miyamura patent. Dr. Miyamura states that the Miyamura patent arose from a collaboration between himself and his colleague Dr. Izumi Saito, with Dr. Houghton and his colleagues at Chiron. Miyamura Decl. ¶5. Dr. Miyamura declares that Dr. Houghton provided him with the HCV-1 ORF sequence shown in Miyamura Figure 12 and the information regarding the HCV-1 putative genomic

organization shown in Miyamura Figure 11.[8] *Id.* at ¶6. Dr. Miyamura further states that neither he nor his colleague Dr. Saito independently determined this information prior to the filing of the applications for the Miyamura patent. *Id.* Dr. Miyamura further declares that the sentence at Miyamura column 17, lines 17-21[9] "reflects work done by Dr. Houghton and his colleagues, not by Dr. Saito and myself. I believe that sentence was the contribution of Dr. Houghton." *Id.* at ¶7.

Applicants also point to the Declaration for Continuation-in-Part Application submitted to the PTO by Drs. Houghton, Choo and Kuo when the application for the '017 patent was filed, a copy of which is attached as Exhibit B hereto. In that declaration Drs. Houghton, Choo and Kuo declare that they are the "original, first and joint" inventors of the subject matter which is claimed and for which a patent is sought. Exhibit B hereto.

(ii) The Legal Standard For Section 102(e) Prior Art

As discussed above, a patent cannot be relied upon as prior art under 35 U.S. C. § 102(e) when the record establishes that the relevant disclosure relied upon in the rejection is the applicant's own work, and furthermore that the relevant portions of the reference patent were obtained from the

[8] Applicants note that the sequence information in Figure 12 of the Miyamura patents and the genomic organization information in Figure 11 of the Miyamura patents together provide the subject matter at Miyamura '928 patent, column 7, lines 8-9 (*i.e.*, prediction of a putative NS3 domain from about amino acid 1007 to about amino acid 1650). First, the differing numbering schemes of Figures 11 and 12 must be normalized to one another. In Figure 12, the first nucleotide of the first translated codon (part of the "putative initiator methionine") is numbered as nucleotide *320*. In contrast, the first nucleotide of the first translated codon in Figure 11 corresponds nucleotide *1*. This may be deduced, for example, because: (a) the protein encoded by the putative C domain is described as having approximately 115 amino acids (Miyamura '928 patent, column 6, line 67 to column 7, line 2); (b) the 3' boundary of the C domain in Figure 11 is designated as nucleotide 345; and (c) since a codon consists of three nucleotides, the first nucleotide of Figure 11 must represent the first nucleotide of the first translated codon (*i.e.*, 3 x 115 = 345). A nucleotide in Figure 11 can thus be correlated to a nucleotide in Figure 12 by adding 319.

The Figure 11 putative boundary numbers (which are all divisible by three) must each represent the final nucleotide of a putative domain, because nucleotide 345 corresponds to the final nucleotide of a 115-amino acid reading frame. Thus, the designation "3018 nt" indicates the final nucleotide of the final codon of NS2. Further, adding 319 to nucleotide 3019 of Figure 11 yields nucleotide 3338 of Figure 12, which corresponds to amino acid 1007. Similarly, the designation "4950 nt" indicates the last nucleotide of the last codon of the putative NS3 domain. Adding 319 to nucleotide 4950 in Figure 11 yields nucleotide 5269 in Figure 12, which corresponds to amino acid 1650. Thus, the putative amino acid range for NS3 disclosed at Miyamura '928 patent, column 7, lines 8-9, corresponds exactly to the nucleotide numbers of Miyamura Figure 11.

[9] At column 17, lines 17-21, the Miyamura '928 patent recites: "Due to the observed similarities between HCV and the Flaviviruses, deductions concerning the approximate locations of the corresponding protein domains and functions in the HCV polyprotein are possible."

applicant. *See* MPEP § 2136.05; *In re Mathews*, 408 F.2d 1393, 161 USPQ 276 (CCPA 1969); *In re Land*, 368 F.2d 886, 151 USPQ 621 (CCPA 1966). "When the 102(e) reference patentee got knowledge of the applicant's invention from him, as by being associated with him . . . and *thereafter* describes it, he necessarily files the application *after* applicant's invention date . . . ." *Mathews*, 408 F.2d at 1396, 161 USPQ at 279 (quoting *Land*, 368 F.2d at 879, 151 USPQ at 633 (emphasis in original)).

(iii) The Subject Matter Of Figures 11 and 12 and at Column 7, lines 8-10 and Column 17, lines 5-21 of the Miyamura Patent Is Not Citable As Prior Art

Applicants respectfully submit that the record here cannot support a conclusion that the Miyamura HCV-1 subject matter[10] relied upon in the Office Action is the invention of "another:"

- The Miyamura patents do not claim the claimed subject matter of the instant application.
- A collaboration between Dr. Houghton and Drs. Miyamura and Saito is evidenced by the recorded assignment for Serial No. 408,045 (the earliest-filed application from which Miyamura claims the benefit of filing date), which is attached as Exhibit I to this Response. In that assignment, Drs. Miyamura and Saito assign their rights in the invention to Chiron Corporation as a co-assignee with the Director General of the National Institute of Health of Japan. Further evidencing a collaboration is the fact that Michael Houghton is named as a joint inventor on U.S. patent application Serial No. 637,380, filed January 4, 1991, for the Miyamura patent. This establishes a collaboration in connection with the September 15, 1989 filing date of Serial No. 408,045 (which included the subject matter relied upon in the Office Action but did not name Dr. Houghton as a joint inventor).
- Prior to the earliest filing date of Miyamura (September 15, 1989), similar or identical subject matter appeared in applications filed by the inventive entity of the instant application). *See* United States patent application Serial No. 07/355,002, filed May 18,

1989 (the '002 application")[11], Figures 62, 62.1 and 62.2 (corresponding to Miyamura Figure 12); page 45, lines 8-13 (corresponding to Miyamura patent at column 17, lines 16-21); and page 123, line 26 (corresponding approximately to Miyamura Figure 11, and Miyamura patent at column 7, lines 8-9).[12] The '002 application was incorporated by reference in the earliest-filed Miyamura application.[13] The European counterpart of the '002 application is incorporated by reference in Miyamura (*i.e.*, EP 388,232). Miyamura patent, column 5, lines 37-44.

- The declaration by the inventors of the '002 patent application, submitted when that application was filed, in which they averred that they were the "original, first and joint inventors . . . of the subject matter which is claimed and for which a patent is sought . . ." (copy attached as part of Exhibit F to this Response).
- Prior to the earliest filing date of Miyamura (September 15, 1989), HCV1 polynucleotide sequences in the HCV NS3 region appeared in applications filed by the inventive entity of the instant application. *See* Figures 32 and 47, EP 318,216 to Houghton et al.[14] The '216 application is incorporated by reference in the Miyamura patent. *See* Miyamura patent, column 5, lines 37-44.

Applicants believe that these facts prevent a conclusion that the Miyamura subject matter at issue is that of "another."

The Miyamura Declaration, coupled with the declaration by the inventors of the '017 patent (and the instant application) that was filed with the application for the '017 patent, further supports that the Miyamura HCV-1 disclosure relied upon by the Examiner was obtained by the Miyamura

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[10] The subject matter at issue is the Miyamura '928 patent disclosure pertaining to the HCV-1 ORF sequence (Figure 12), the putative genomic organization of HCV-1 (Figure 11 and column 7, lines 8-9), and column 17, lines 17-21.

[11] This application was incorporated by reference into Serial No. 07/456,637 (Exhibit D hereto, page 1, lines 10-12; page 2, lines 2-3), which itself was incorporated by reference into the '017 patent (*see, e.g.*, '017 patent, column 2, lines 43-49).

[12] For the convenience of the Examiner a copy of the following from the '002 application is attached as Exhibit F to this Response: Figure 62, 62-1 and 62-2, and pages 17 (describing Figure 62), 45 and 123. Also attached as Exhibit F to this Response is a copy of the Filing Receipt for the '002 application, showing the inventorship.

[13] *See* page 8, lines 3-4 of the 'Miyamura '045 application, attached as Exhibit G to this Response.

[14] For the convenience of the Examiner a copy of the following from the '216 application is attached as Exhibit J to this Response: Page 1, page 9 (describing Figures 32 and 47), and Figures 32-1 to 32-7 and 47-1 to 47-8.

inventors from the inventors of the instant application (through Dr. Houghton), and that this disclosure was the own work of the inventors of the instant application. *See Mathews*, 408 F.2d at 1396; Exhibits A & B hereto. Accordingly, the portions of the Miyamura patent pertaining to the HCV-1 ORF sequence (Figure 12), putative genomic organization of HCV-1 (Figure 11 and column 7, lines 8-9 of the Miyamura patent), and column 17, lines 17-21 of the Miyamura patent, have effectively been removed as prior art under 35 U.S.C. § 102(e).

c. The Disclosure in Miyamura of Methods of Production of Polypeptides Encoded by the HCV Genome, Taken Alone, Does Not Render Claims 27-35 Obvious

The Office Action also relies upon "Examples I-IV at columns 28-39" to contend that Miyamura et al. "teach preparation of cloning vectors, and transformed host cells comprising the vectors, comprising inserts of specific, defined, regions found anywhere in a nucleic acid sequence encoding all or part of an hepatitis C virus polyprotein." Office Action, page 11. The patent "explicitly teach, at cols. 8-10, that expression vectors comprising transcriptional and translational regulatory elements operably linked to a polynucleotide encoding a desired regions [sic] of the HCV polyprotein should be used to produce desired portions of the hepatitis C virus polyprotein in host cells." *Id.* Miyamura et al. "further suggest preparation of expression constructs providing fusions of hepatitis C virus amino acid sequence regions with proteins commonly used in the art as fusion partners such as β-galactosidase and superoxide dismutase [SOD]." Office Action, page 11 (bracketed text in original).

As shown above, there is no HCV protease sequence in Miyamura that is citable as prior art against the instant application. Absent a prior art HCV protease sequence to be expressed, disclosure concerning standard methodology for expressing polypeptides cannot by itself support a *prima facie* obviousness rejection.

d. The Rejection Must Be Withdrawn Based on the Removal of the Subject Matter of Figures 11 and 12, Column 17, lines 17-21, and Column 7, lines 8-9, of the Miyamura Patent.

The Miyamura patent cannot support a *prima facie* obviousness rejection because, as shown above, the key disclosures thereof are not available as prior art. Applicants submit that the outstanding rejection must be withdrawn in the absence of the subject matter derived from the inventors of the instant application. The secondary references on which the Examiner relies—Gorbalenya, Bazan and Miller—do not remedy Miyamura's deficiencies.

Gorbalenya and Bazan concern flaviviruses. Neither reference mentions HCV, and HCV is not a flavivirus.[15] Miller discloses only nucleic acid sequence of a helicase region within the NS3 domain of HCV. Miller does not disclose any sequence encoding a protease. Thus, there is no link between Gorbalenya, Bazan or Miller to the pending claims of the instant application. In view of the foregoing, none of the secondary references cited by the Examiner can support a *prima facie* obviousness rejection.[16]

[15] Miyamura itself states that HCV is "a new viral class" distinct from flaviviruses. *See, e.g.,* Miyamura '928 patent, column 2, lines 1-8; *see also* C. Rice, "Flaviviridae -- The Viruses And Their Replication", in Fields Virology, Vol. 1 (B. Fields) (3d ed. 1995), pages 932-33, which is attached as Exhibit C to this Response.

[16] For the record, applicants do not concede that the claims are *prima facie* obvious over Miyamura in view of Gorbalenya, Bazan and Miller even if the HCV-1 subject matter of Miyamura is legally available as a prior art reference (which it is not).

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002010005. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 10, 2005

Respectfully submitted,

By _____

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